The functional genetic link of NLGN4X knockdown and neurodevelopment in neural stem cells.

Journal: Hum Mol Genet

Publication Year: 2013

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PubMed link: 23710042

Funding Grants: Regulation of human neural progenitor cell proliferation by Ryk-mediated Wnt signaling, Defining the molecular mechanisms of somatic cell reprogramming

Public Summary:
This work is to use human ipS cells to model huamn autisms by knockdown of NLGN4X.

Scientific Abstract:
Genetic mutations in NLGN4X (neuroligin 4), including point mutations and copy number variants (CNVs), have been associated with susceptibility to autism spectrum disorders (ASDs). However, it is unclear how mutations in NLGN4X result in neurodevelopmental defects. Here, we used neural stem cells (NSCs) as in vitro models to explore the impacts of NLGN4X knockdown on neurodevelopment. Using two shRNAmir-based vectors targeting NLGN4X and one control shRNAmir vector, we modulated NLGN4X expression and differentiated these NSCs into mature neurons. We monitored the neurodevelopmental process at Weeks 0, 0.5, 1, 2, 4 and 6, based on morphological analysis and whole-genome gene expression profiling. At the cellular level, in NSCs with NLGN4X knockdown, we observed increasingly delayed neuronal development and compromised neurite formation, starting from Week 2 through Week 6 post differentiation. At the molecular level, we identified multiple pathways, such as neurogenesis, neuron differentiation and muscle development, which are increasingly disturbed in cells with NLGN4X knockdown. Notably, several postsynaptic genes, including DLG4, NLGN1 and NLGN3, also have decreased expression. Based on in vitro models, NLGN4X knockdown directly impacts neurodevelopmental process during the formation of neurons and their connections. Our functional genomics study highlights the utility of NSCs models in understanding the functional roles of CNVs in affecting neurodevelopment and conferring susceptibility to neurodevelopmental diseases.